

# Is Red Cell Distribution Width a Marker for the Presence and Poor Prognosis of Cardiovascular Disease?

## *Kırmızı Kan Hücre Dağılım Genişliği Kardiyovasküler Hastalık Varlığı ve Kötü Gidişatı için Bir Gösterge midir?*

Turgay Isik<sup>1</sup>, Erkan Ayhan<sup>1</sup>, Mustafa Kurt<sup>2</sup>, Ibrahim Halil Tanboga<sup>3</sup>, Ahmet Kaya<sup>2</sup>, Enbiya Aksakal<sup>3</sup>

<sup>1</sup>Department of Cardiology, Faculty of Medicine, Balıkesir University, Balıkesir, Turkey

<sup>2</sup>Department of Cardiology, Erzurum Education and Research Hospital, Erzurum, Turkey

<sup>3</sup>Department of Cardiology, Faculty of Medicine, Ataturk University, Erzurum, Turkey

### Abstract

Red cell distribution width (RDW) is an indices heterogeneity of cell size in the peripheral blood and has been shown to be an independent correlate of adverse outcomes in healthy subjects and in some cardiac conditions. Additionally, RDW is associated with both the presence and the complexity of vascular disease. In this review we investigate the importance of RDW in vascular disease in the light of recent information.

**Key Words:** Acute cardiovascular events, Cardiovascular disease, Red cell distribution width

### Özet

Kırmızı kan hücre dağılım genişliği (KKHDG) periferik dolaşım sisteminde farklı kırmızı kan hücre boyutlarının bir göstergesi olup, sağlıklı insanlarda ve bazı kardiyak bozukluklarda kötü gidişat ile bağımsız şekilde ilişkili olduğu gösterilmiştir. Ayrıca, KKHDG'nin gerek vasküler hastalığının varlığı gerekse kompleksitesi ile ilişkili olduğu gösterilmiştir. Bu yazımızda KKHDG'nin vasküler hastalıktaki önemini son bilgiler ışığında değerlendirdik.

**Anahtar Kelimeler:** Akut kardiyovasküler olaylar, Kardiyovasküler hastalık, Kırmızı kan hücre dağılım genişliği

### Introduction

Red cell distribution width (RDW) is a measure of the variability in the size of circulating erythrocytes (anisocytosis) [1]. Elevated RDW levels can be observed in many clinical conditions, such as hemolysis, after blood transfusions and in response to ineffective red cell production, which can be caused by deficiencies in iron, vitamin B12 or folate. RDW is also increased in certain clinical states, such as pregnancy, thrombotic thrombocytopenic purpura and inflammatory bowel disease. Due to a lack of knowledge regarding its historical prognostic significance, RDW has previously been ignored beyond the evaluation of anemia.

Recently, many studies have revealed that the baseline RDW value has been shown to be associated with long term adverse events in both acute and chronic conditions, such as acute myocardial infarctions (MI), heart failures, stable angina, stroke, and peripheral artery disease, as well as in patients who are free of coronary disease [2-8]. These results were observed even after adjusting for multiple potential

confounders, including anemia. Additionally, RDW is associated with both the presence and complexity of coronary artery disease (CAD) [9]. In this review, we investigate the importance of RDW in vascular disease by considering the recent literature.

### Healthy subjects and RDW

Previous studies reported that RDW was associated with poor prognosis rather than simply with vascular disease. Chen et al. [8] concluded that elevated RDW values were associated with an increased risk of all-cause mortality in patients without known heart disease. Furthermore, Perlstein et al. [7] showed that RDW strongly predicted all-cause and cardiovascular mortality. Similarly, Patel et al. [10] demonstrated that RDW was a powerful predictor of mortality in older adults with and without major age-associated diseases.

### Stable vascular disease and RDW

Red cell distribution width is a significant prognostic marker for stable vascular disease. Lappe et al. [11] demon-

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Correspondence to: Turgay Isik, Department of Cardiology, Faculty of Medicine, Balıkesir University, Cagis Campus, Balıkesir, Turkey

Phone: +90 266 612 14 55 Fax: +90 266 612 14 59 e-mail: isikturgay@yahoo.com

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strated that RDW was associated with mortality in patients with stable coronary disease and in normal coronary subjects. Similarly, Tonelli et al. [4] showed that elevated RDW was associated with the risk of heart failure, cardiovascular events and all-cause death in patients who had experienced prior MI but who were not currently symptomatic for heart failure. In addition, RDW is also an independent prognostic factor for patients with peripheral arterial disease. In one study, a 10% increased risk of mortality was observed with a 1% increase in RDW [6]. In our study, we reported that a greater baseline RDW value was independently associated with both the presence of CAD and a greater coronary complexity of CAD, as assessed by the SYNTAX score. We compared patients with high ( $\geq 32$ ) and moderate to low ( $< 32$ ) SYNTAX scores. The group with high SYNTAX scores presented significantly elevated RDW values. RDW, age and obesity were identified as independent correlates of a high SYNTAX score [12]. In addition, it has been well established that coronary complexity is associated with a poor prognosis [13].

#### Acute vascular events and RDW

Beyond stable vascular diseases, RDW is also related to the prognosis of acute vascular conditions. Azab et al. [14] showed that higher RDW was a strong and independent predictor of in-hospital and long-term mortality in patients with non-STEMI. Uyarel et al. [2] reported that in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI, a high RDW level upon admission was associated with an increased risk for in-hospital and long-term cardiovascular events and mortality. They reported that an RDW level  $> 14.8\%$  at admission was an independent predictor of long term cardiovascular mortality across the entire cohort or in the nonanemic subpopulation of patients. The study showed that the mean left ventricular ejection fraction and the success rate of surgical procedures were lower in patients with an elevated RDW [2]. Similarly, we demonstrated that the baseline RDW level was found to be an independent predictor of the 6-month cardiovascular mortality after primary PCI. Furthermore, we showed for the first time that baseline RDW levels were significantly increased in patients with inadequate ST-segment resolution (electrocardiographic non-reflow) after primary PCI and that the baseline RDW level was an independent predictor for this condition [15]. Ani et al. [5] showed that the mean RDW was significantly higher among patients who had experienced a stroke compared to those who had not experienced a stroke.

#### Heart failure and RDW

Heart failure (HF) is an epidemiologic condition, and its prevalence is increasing. Borne et al. [16] showed that RDW was associated with the incidence of first hospitalization

due to HF among 26,784 middle-aged subjects who had not yet presented MI, stroke, or HF. Roland et al. [17] noted that RDW was frequently elevated among patients with acute HF and independently predicts one year mortality in acute HF. Similarly, Allen et al. [18] reported that RDW was a strong, independent predictor of adverse outcome in patients with chronic heart failure.

The mechanistic links between RDW and the presence and poor prognosis of cardiovascular disease is not yet fully understood. Several mechanisms have been suggested to explain the exact role of RDW in cardiovascular disease. It is well known that a close relationship exists between elevated RDW levels and a number of symptoms that have prognostic importance in cardiovascular disease, such as decreased kidney function [19]. Another study demonstrated that RDW was associated with the level of complexity of CAD [9]. Many studies have reported that elevated RDW values were associated with high inflammatory (such as hs-CRP) [11, 20] and neurohumoral (such as B-type natriuretic peptide) markers and low anti-oxidative indices (such as selenium) [21, 22]. Inflammation possibly contributes to an increased RDW by impairing iron metabolism, inhibiting the production of or response to erythropoietin and shortening red blood cell survival [23]. Moreover, in previous studies, inflammatory cytokines have been found to suppress the maturation of erythrocytes; immature erythrocytes then enter into the circulation and may accelerate erythropoiesis [24]. Oxidative stress was proposed as another mechanism of the prognostic value of RDW [18, 25]. Red blood cells have a powerful anti-oxidant capacity and serve as a primary oxidative sink; they are prone to oxidative damage, which reduces cell survival, and they enhance the release of juvenile erythrocytes into circulation. Consequently, we propose that the link between increased oxidative stress, inflammatory activation and an elevated RDW value is closely related to the presence and poor prognosis of cardiovascular disease.

In conclusion, as an inexpensive index that is routinely reported as a part of the complete blood count, RDW is an important marker for both diagnostic and prognostic purposes in various clinical cardiovascular settings.

**Conflict of interest statement:** The authors declare that they have no conflict of interest to the publication of this article.

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